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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/036,224	11/09/2001	Stefan Peters	I/1165	5256
28501	7590	06/22/2004	EXAMINER	
BOEHRINGER INGELHEIM CORPORATION			SHIAO, REI TSANG	
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P. O. BOX 368			ART UNIT	
RIDGEFIELD, CT 06877			PAPER NUMBER	
			1626	

DATE MAILED: 06/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/036,224

Applicant(s)

PETERS ET AL.

Examiner

Robert Shiao

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on application filed on 11/09, 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) _____ is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-24 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

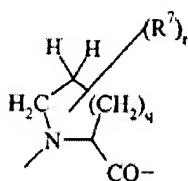
DETAILED ACTION

1. Claims 1-24 are pending in the application.

Election/Restriction

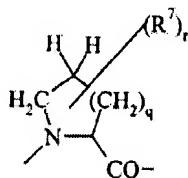
2. The Markush group set forth in the claims includes both independent and distinct inventions, and patentably distinct compounds (or species) within each invention. However, this application discloses and claims a plurality of patentably distinct inventions far too numerous to list individually. Moreover, each of these inventions contains a plurality of patentably distinct compounds, also far too numerous to list individually. For these reasons provided below, restriction to one of the following Groups is required under 35 U.S.C. 121, wherein an Group is a set of patentably distinct inventions of a broad statutory category (e.g. Compounds, Methods of Use, Methods of Making, etc.):

- I. Claims 1-15, and 19-20, in part, drawn to compounds/compositions of formula (I), wherein the variable Cyt' represents cytotoxic compound doxorubicin thereof; the variable R³ does not represent heteroaryl, and the variable R^a and R^b together with the interjacent N-C group form a hetrocycle ring pyrrolidine thereof; the variable R¹ represents Cg-A, Cg-B-A or Cg(D)n-B-A, wherein the variable Cg represents R²-(CH₂)_m-Z-, the variable Z is -CO-, -O-CO-, SO₂, NH-CO- or a single bond, the variable m is 0, 1, or 2, the variable R² is selected from pyridine thereof, the cyclic amino carboxylic acid of the formula



of the variables A, B, and D, wherein the variable q is 1, R^7 is as defined in claim 4, the R^4 , R^5 , and R^6 of variables A, B, and D do not independently represent heteroaryl thereof, classified in classes 546, numerous subclasses. If this group is elected, applicants are requested to elect a single species for the search purpose. It is noted that the limitation of variable R^a and R^b are not defined.

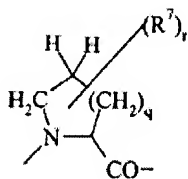
- II. Claims 1-15, and 19-20, in part, drawn to compounds/compositions of formula (I), wherein the variable Cyt' represents cytotoxic compound doxorubicin thereof; the variable R^3 does not represent heteroaryl, and the variable R^a and R^b together with the interjacent N-C group form a hetrocycle ring pyrrolidine thereof; the variable R^1 represents Cg-A, Cg-B-A or Cg(D)n-B-A, wherein the variable Cg represents $R^2-(CH_2)_m-Z$, the variable Z is $-CO-$, $-O-CO-$, SO_2 , $NH-CO-$ or a single bond, the variable m is 0, 1, or 2, the variable R^2 is selected from morpholine, pyrazine, or piperidine thereof, the cyclic amino carboxylic acid of the formula



of the variables A, B, and D, wherein the variable q is 1, R^7 is as defined in claim 4, the R^4 , R^5 , and R^6 of variables A, B, and

D do not independently represent heteroaryl thereof, classified in classes 544/546, numerous subclasses. If this group is elected, applicants are requested to elect a single species for the search purpose. It is noted that the limitation of variable R^a and R^b are not defined.

- III. Claims 1-15, and 19-20, in part, drawn to compounds/compositions of formula (I), wherein the variable Cyt' represents cytotoxic compound doxorubicin thereof; the variable R^3 does not represent heteroaryl, and the variable R^a and R^b together with the interjacent N-C group form a hetrocycle ring pyrrolidine theeof; the variable R^1 represents Cg-A, Cg-B-A or Cg(D)n-B-A, wherein the variable Cg represents $R^2-(CH_2)_m-Z-$, the variable Z is $-CO-$, $-O-CO-$, SO_2 , $NH-CO-$ or a single bond, the variable m is 0, 1, or 2, the variable R^2 is selected from thiazole, imidazole, or pyrrolidine thereof, the cyclic amino carboxylic acid of the formula



of the variables A, B, and D, wherein the variable q is 1, R^7 is as defined in claim 4, the R^4 , R^5 , and R^6 of variables A, B, and D do not independently represent heteroaryl thereof, classified in classes 548, numerous subclasses. If this group is elected, applicants are requested to elect a single species for the search purpose. It is noted that the limitation of variable R^a and R^b are not defined.

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- IV. Claims 1-15, and 19-20, in part, drawn to compounds/compositions of formula (I), receiving compounds not encompassed in Groups I-III, classified in classes 544/546/548, numerous subclasses. If this group is elected, applicants are requested to elect a single species for the search purpose. This group is subject further restriction if it is elected.
- V. Claims 16-20, in part, drawn to product prodrug, classified in classes 514/544/546/548, numerous subclasses. If this group is elected, applicants are requested to elect a single species for the search purpose. This group is subject further restriction if it is elected.
- VI. Claims 21-24, drawn to method of use (i.e., treating cancer), classified in classes 514, numerous subclasses. If this group is elected, applicants are requested to elect a single species for the search purpose.

If Group VI is elected, then election of one of the following methods of use is required:

- A. Method of treating breast cancer
 - B. Method of treating colorectal cancer
 - C. Method of treating ovarian cancer
- and etc.

In accordance with the decisions in *In re Harnisch*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984), restriction of a Markush group is proper where the compounds within the group either (1) do not share a common utility, or (2) do not share a substantial structural feature disclosed as being essential to that utility. In addition, a Markush group may encompass a plurality of independent and distinct inventions where two or more members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the other member(s) obvious under 35 U.S.C. 103.

Where an election of any one of Groups I-VI is made, an election of a single compound or species is further required. Moreover, an election of a single compound is further required including an exact definition of each substitution on the base molecule (Formula 1), wherein a single member at each substituent group or moiety is selected. For example, if a base molecule has a substituent group R^3 , wherein R^3 is recited to be any one of hydrogen, alkyl, aryl, etc., then applicant must select a single substituent of R^3 , for example phenyl, and each subsequent variable position. Should applicant traverse on the ground that the compounds are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the compounds to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C 103(a) of the other.

All compounds falling outside the class(es) and subclass(es) of the selected compound and any other subclass encompassed by the election above will be directed to nonelected subject matter and will be withdrawn from consideration under 35 U.S.C. 121 and 37 C.F.R. 1.142(b). Applicant may reserve the right to file divisional applications on the remaining subject matter. The provisions of 35 U.S.C. 121 apply with regard to double patenting covering divisional applications.

Applicant is reminded that upon cancellation of claims to a non-elected invention, the inventors must be amended in compliance with 37C.F.R. 1.48(b) if one of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 C.F.R. 1.48(b) and by the fee required under 37CFR 1.17(i).

If desired upon election of a single compound, applicants can review the claims and disclosure to determine the scope of the invention and can **set forth** a group of compounds which are so similar within the same inventive concept and reduction to practice. Markush claims must be provided with support in the disclosure for each member of the Markush group. See MPEP 608.01(p). Applicant should exercise caution in making a selection of a single member for each substituent group on the base molecule to be consistent with the written description.

Rationale Establishing Patentable Distinctiveness Within Each Group

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Each Invention Set listed above is directed to or involves the use or making of compounds which are recognized in the art as being distinct from one another because of their diverse chemical structure, their different chemical properties, modes of action, different effects and reactive conditions (MPEP 806.04, MPEP 808.01). Additionally, the level of skill in the art is not such that one invention would be obvious over either of the other inventions, i.e. they are patentable over each other. Chemical structures which are similar are presumed to function similarly, whereas chemical structures that are not similar are not presumed to function similarly. The presumption even for similar chemical structures though is not irrebuttable, but may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have been expected to function as the structure of the claimed invention. Note that in accordance with the holdings of Application of Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Lalu, 223 USPQ 1257 (Fed. Cir. 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

The above Groups represent general areas wherein the inventions are independent and distinct, each from the other because of the following reasons:

Each of Groups I- V are distinct and independent products, one from the other on the basis of structure defined in the claimed compounds as directed to various compound of formula (I) of claim 1 having various heteroaryl or

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heterocycle (i.e., thiazole, thiadiazole, pyridyl, oxazole, pyrimidine, etc). Absent factual evidence to the contrary, each is a different chemical compound.

Groups I-V and VI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using the product (MPEP 806.05(h)). In the instant case, the morpholine compounds as claimed can be used in a materially different process of using, i.e., tachykinin antagonists, see US 5,612,336 or CAS:120:298471. The instant morpholine compounds are as demonstrated throughout the specification and in claims 1-24 which are directed to several different methods of using the morpholine compounds, for example treating cancer.

In addition, because of the plethora of classes and subclasses in each of the Groups, a serious burden is imposed on the examiner to perform a complete search of the defined areas. Therefore, because of the reasons given above, the restriction set forth is proper and not to restrict would impose a serious burden in the examination of this application.

Advisory of Rejoinder

3. The following is a recitation of M.P.E.P. §821.04, Rejoinder:

Where product and process claims drawn to independent and distinct inventions are presented in the same application, applicant may be called upon under 35 U.S.C. 121 to elect claims to either the product or process. See MPEP § 806.05(f) and § 806.05(h). The claims to the nonelected invention will be withdrawn from further consideration under

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37 CFR 1.142. See MPEP § 809.02 (c) and § 821 through § 821.03. However, if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined.

Where product and process claims are presented in a single application and that application qualifies under the transitional restriction practice pursuant to 37 CFR 1.129(b), applicant may either (1) elect the invention to be searched and examined and pay the fee set forth in 37 CFR 1.17(s) and have the additional inventions searched and examined under 37 CFR 1.129(b)(2), or (2) elect the invention to be searched and examined and not pay the additional fee (37 CFR 1.129(b)(3)). Where no additional fee is paid, if the elected invention is directed to the product and the claims directed to the product are subsequently found patentable, process claims which either depend from or include all the limitations of the allowable product will be rejoined. If applicant chooses to pay the fees to have the additional inventions searched and examined pursuant to 37 CFR 1.129(b)(2), even if the product is found allowable, applicant would not be entitled to a refund of the fees paid under 37 CFR 1.129(b) by arguing that the process claims could have been rejoined. 37 CFR 1.26 states that "money paid by actual mistake or in excess will be refunded, but a mere change of purpose after the payment of money...will not entitle a party to demand such a return..." The fees paid under 37 CFR 1.129(b) were not paid by actual mistake nor paid in excess, therefore, applicant would not be entitled to a refund.

In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104 - 1.106. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. If the application containing the rejoined claims is not in condition for allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action.

The following is a recitation from paragraph five, "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. §103(b)" (1184 TMOG 86(March 26, 1996)):

"However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim **depends from or otherwise includes all the limitations of** an allowed product claim. Withdrawn process claims not commensurate in scope with an allowed product claim will not be rejoined." (emphasis added)

Therefore, in accordance with M.P.E.P. §821.04 and *In re Ochiai*, 71 F.3d 1565, 37 USPQ 1127 (Fed. Cir. 1995), rejoinder of product claims with process claims commensurate in scope with the allowed product claims will occur following a finding that the product claims are allowable. Until, such time, a restriction between product claims and process claims is deemed proper. Additionally, in order to retain the right to rejoinder in accordance with the above

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policy, Applicant is advised that the process claims should be amended during prosecution to maintain either dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Shiao whose telephone number is (571) 272-0707. The examiner can normally be reached on 8:30 AM - 5:00 PM.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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R.S.

Robert Shiao, Ph.D.
Patent Examiner
Art Unit 1626

for 

Joseph K. McKane
Supervisory Patent Examiner
Art Unit 1626

June 17, 2004